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MINI-REVIEW

The role of Macklin effect in management of ARDS: beyond spontaneous pneumomediastinum

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Abstract

Barotrauma (including pneumomediastinum, pneumothorax or subcutaneous emphysema) is a frequent complication of patients with acute respiratory distress syndrome (ARDS) and is associated with worse outcome. Furthermore, some Authors hypothesize that pneumomediastinum could be a sign of ongoing patient self-inflicted lung injury (P-SILI) in patients with respiratory failure receiving non-invasive respiratory support. It has been recently found that a well-known radiological sign, the Macklin effect (or pulmonary interstitial emphysema), could be a powerful predictor of subsequent development of barotrauma in patients with ARDS (sensitivity = 89.2% (95% confidence interval (CI): 74.6 to 96.9); specificity = 95.6% (95% CI: 90.6 to 98.4)). Of note, Macklin effect is visible on chest computed tomography (CT) scan 8–12 days before overt barotrauma. Furthermore, patients with Macklin effect not currently receiving invasive ventilation have a high risk of subsequent intubation. Accordingly, it could be hypothesized that Macklin effect could be a marker of lung fragility, disease severity, and P-SILI in patients with ARDS. Therefore, detection of Macklin effect on chest CT scan could be used to stratify baseline risk of patients with ARDS, select which patients should be evaluated for alternative management algorithms, including advanced respiratory monitoring, ultraprotective ventilation, or institution of extracorporeal support without invasive ventilation.

Keywords

Acute respiratory distress syndrome; Mechanical ventilation; Pneumothorax; Pneumomediastinum; Extracorporeal membrane oxygenation; Ventilator-induced lung injury; Barotrauma; Macklin effect

1. Background

Barotrauma, spanning from asymptomatic small pneumomediastinum to life-threatening massive pneumothorax, occurs relatively frequently in patients with acute respiratory distress syndrome (ARDS). The occurrence rate of barotrauma may be particularly high in patients requiring invasive ventilation due to coronavirus disease 2019 (COVID-19) ARDS, with a reported rate of about 15% [1]. Unfortunately, development of barotrauma is associated with high mortality rates (greater than 60% in COVID-19 ARDS patients, around 46% in non-COVID-19 ARDS patients) [1]. Fragility of lung parenchyma represents a major issue in ARDS. In addition, it is well established that in high-risk patients, mechanical ventilation may cause pulmonary damage (ventilator-induced lung injury (VILI)) and potentially induce barotrauma even when optimal, "protective" mechanical ventilation [2, 3] is applied. Furthermore, abnormal breathing patterns and altered respiratory mechanics in spontaneously breathing patients with respiratory failure may worsen lung injury (patient self-inflicted lung injury (P-SILI)) [4]. Indeed, barotrauma occurs also in patients with COVID-19 ARDS not receiving respiratory support [5]. Interestingly, several studies suggest that development of air leak may be a marker of P-SILI in patients with respiratory failure in spontaneous breathing [6, 7]. Early assessment of lung frailty could therefore allow to early stratify the risk of barotrauma susceptibility and potentially P-SILI amongst ARDS patients, providing a rationale for the deployment of protective management strategies in those at high-risk for barotrauma. However, there is no established prediction method in terms of timing, accuracy and easiness.

2. Macklin effect and barotrauma

Macklin effect (also described as pulmonary interstitial emphysema or Macklin-like radiological sign) is a subtle and well-known radiological sign consisting of an air tracking along pulmonary bronchovascular sheaths, interlobular septa and/or visceral pleura [8, 9], easily recognizable on chest computed tomography (CT) scan, irrespective of contrast medium

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administration (Fig. 1). Historically, Macklin-like radiological sign has been used to differentiate between pneumomediastinum due to "central" causes (*e.g.*, lesion to large airways or esophagus) and pneumomediastinum due to "peripheral" causes (*e.g.*, lesion to the alveoli), especially in the context of blunt chest trauma or spontaneous pneumomediastinum [8, 10].

Some Authors recently demonstrated that Macklin effect has a high accuracy in predicting barotrauma in patients with COVID-19 ARDS requiring invasive ventilation, with a specificity of 95.6% (95% confidence interval (CI) = 90.6 to 98.4), and a sensitivity of 89.2% (95% CI = 74.6 to 96.9) [11, 12]. Importantly, the Authors found that Macklin effect is usually already evident on chest CT scan 8 to 12 days before clinically overt barotrauma [11, 12]. They also found that there is a relationship between the time to the first radiological evidence of barotrauma and the topographical distribution of Macklin effect within the lung parenchyma: the larger (and more "central") the bronchovascular sheath involved, the shorter the temporal advance [11]. These results have been confirmed in a study enrolling 698 COVID-19 patients (specificity: 99.85% (95% CI = 99.2 to 100); sensitivity: 100% (95% CI = 89.1 to 100); accuracy: 99.8% (95% CI = 99.2 to 100) [13], as well as from studies from other research groups [14, 15]. The same Author group also published a proof of concept study suggesting that Macklin effect may be used as an early marker to candidate patients for ultraprotective mechanical ventilation or early extracorporeal membrane oxygenation [16].

From a pathophysiological point of view, it is possible that the high respiratory effort (typical of patients with respiratory failure) leads to excessive transpulmonary pressure and hence to rupture of distal airways [4]. Indeed, several studies and Authors now suggest that increased transpulmonary pressure, increase burden of lung disease, and inappropriate management of non-invasive respiratory support may trigger barotrauma in patients with respiratory failure [6, 7, 17–19]. Furthermore, some conditions such as COVID-19 ARDS could increase the risk of alveolar rupture, due to possible formations of microthrombi in the pulmonary vessels, with the potential risk of ischemic damage to alveolar cells superimposed to P-SILI/VILI, and therefore increased lung fragility [7, 20]. However, whether *primum movens* of alveolar rupture is the excessive respiratory effort, fragility of lung parenchyma, or a combination of both, remains at present to be determined.

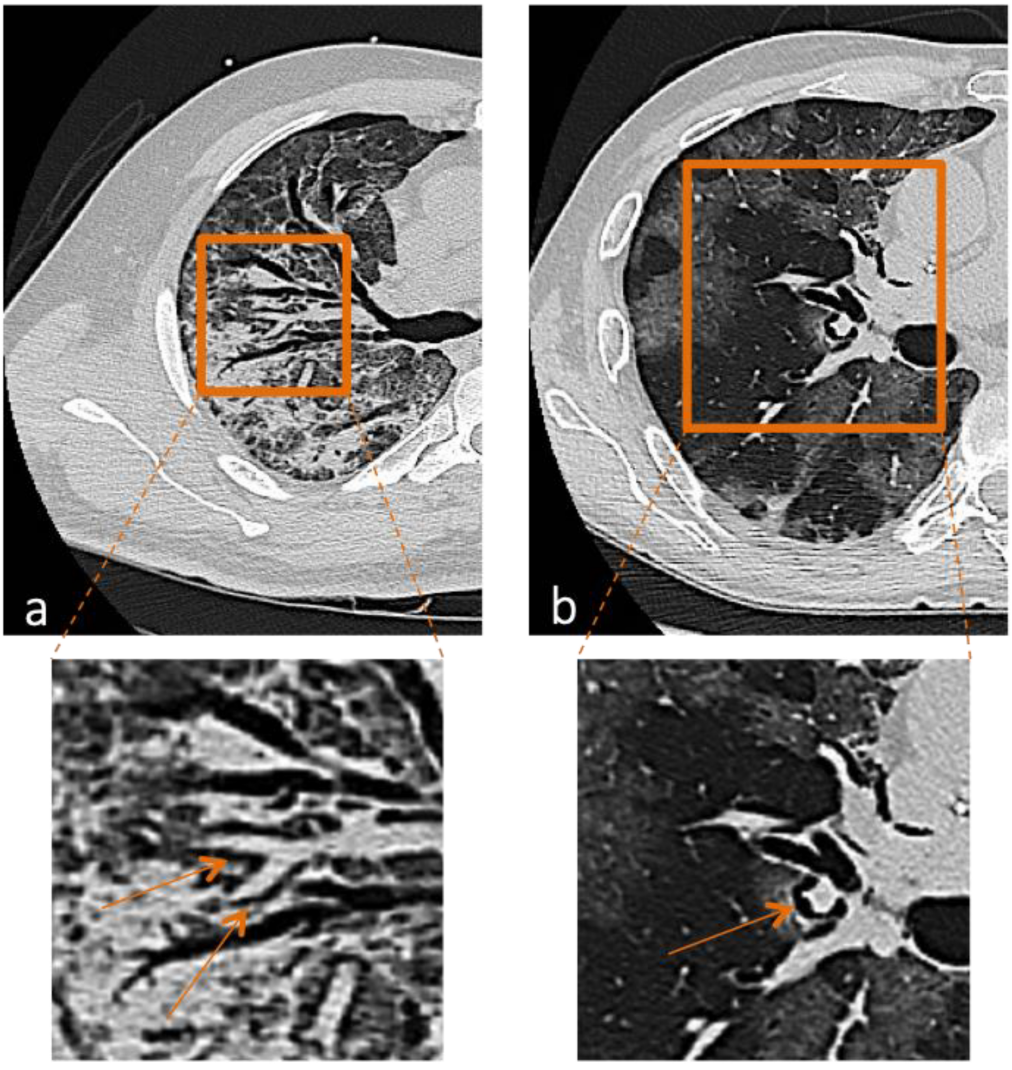

FIGURE 1. Chest CT scan of a patient with Macklin sign. (a) Macklin sign in mid-distal bronchovascular tree. (b) Macklin sign in proximal bronchovascular tree.

3. Clinical applications of Macklin effect in ARDS

Accordingly, it could be hypothesized that detection of Macklin effect might be used to characterize a specific ARDS subphenotype characterized by higher lung fragility and, potentially, greater disease severity. In addition, some Authors hypothesized that occurrence of pneumomediastinum may be a marker of P-SILI in patients undergoing non-invasive respiratory support [6, 18, 19]. As Macklin effect precede clinical and/or radiologically evident pneumomediastinum by several days, it can be speculated that detection of Macklin effect may help in detecting P-SILI.

Management of barotrauma in patients with respiratory failure is difficult, non-standardized and generally involve institution of very low-pressure ventilation or avoidance of invasive ventilation [21]. Detection of Macklin effect might accordingly be used to select high-risk patients for specific management algorithms and/or advanced monitoring (Fig. 2). For example, clinicians might decide to initiate advanced monitoring of respiratory mechanics using esophageal pressure [22–24] in patients receiving non-invasive respiratory support. In addition, patients receiving non-invasive respiratory support may be selected for strategies including awake pronation [25–28] or, alternatively, decision to proceed immediately with invasive, protective mechanical ventilation. An interesting, alternative option for the most severe cases could be the institution of early extracorporeal support without invasive ventilation [16, 29–31]. Patients who are already invasively ventilated could be considered for ultraprotective ventilation combined with early extracorporeal support before meeting suggested criteria for extracorporeal membrane oxygenation [2, 31, 32].

4. Conclusions

The integration of clinical signs, symptoms, respiratory mechanics and radiological findings may ultimately help to develop personalized medicine in ARDS. Clinicians may better identify which patients may be more likely to benefit from implementation (or avoidance) of various management strategies. Furthermore, such integration might contribute to further understand why several promising strategies for ARDS management (*i.e.*, recruitment maneuvers, use of ultraprotective ventilation together with extracorporeal support) did not show improved outcome, or were even associated with harm when assessed in randomized controlled trials [33, 34].

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

AB, DP and GL—designed the research study. AB and DP—drafted the manuscript. MDB, AZ and GL—critically reviewed the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

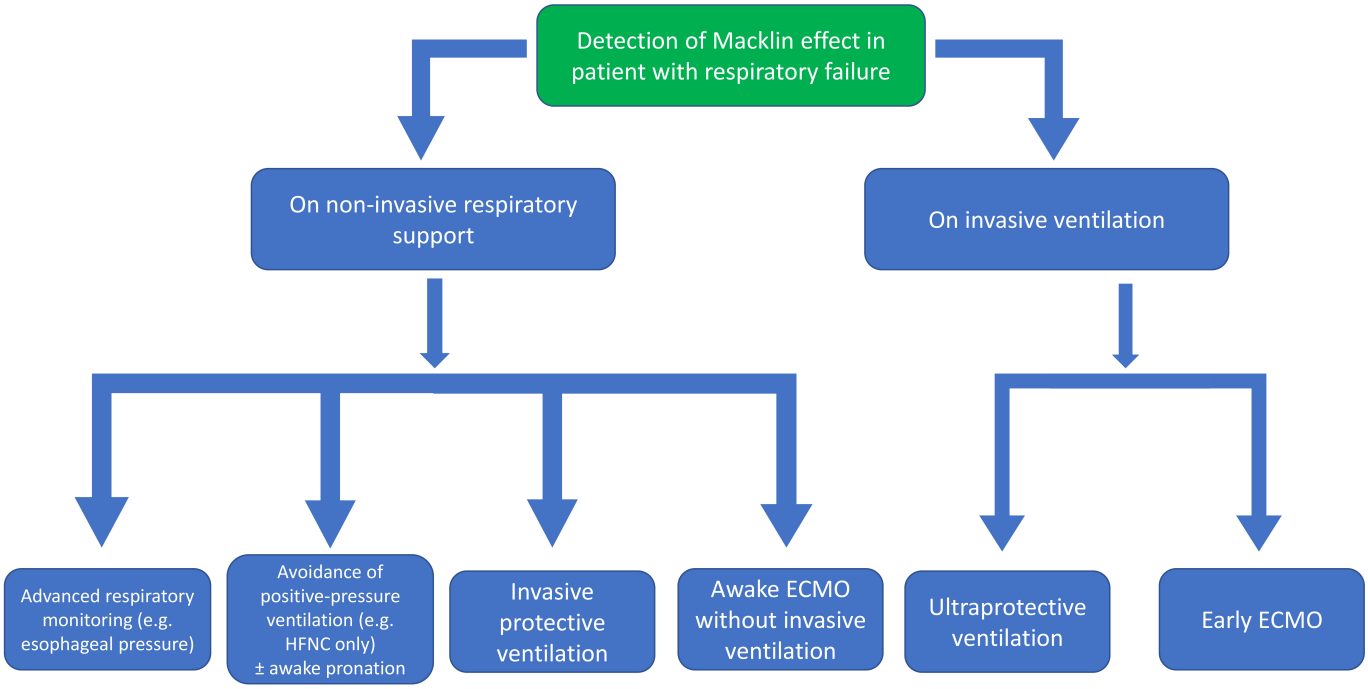
Detection of Macklin effect in patient with respiratory failure
On non-invasive respiratory support
On invasive ventilation
Advanced respiratory monitoring (e.g. esophageal pressure)
Avoidance of positive-pressure ventilation (e.g. HFNC only) ± awake pronation
Invasive protective ventilation
Awake ECMO without invasive ventilation
Ultraprotective ventilation
Early ECMO

FIGURE 2. Hypothetical management algorithm for patients with respiratory failure and evidence of Macklin effect on chest computed tomography scan. HFNC: high-flow nasal cannula; ECMO: extracorporeal membrane oxygenation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Giovanni Landoni is serving as the Editor-in-Chief, Alessandro Belletti is serving as one of the Editorial Board members of this journal. We declare that Giovanni Landoni and Alessandro Belletti had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to OK.

REFERENCES

[1] Belletti A, Todaro G, Valsecchi G, Losiggio R, Palumbo D, Landoni G, *et al*. Barotrauma in coronavirus disease 2019 patients undergoing invasive mechanical ventilation: a systematic literature review. Critical Care Medicine. 2022; 50: 491–500.

[2] Grasselli G, Calfee CS, Camporota L, Poole D, Amato MBP, Antonelli M, *et al*. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Medicine. 2023; 49: 727–759.

[3] Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. American Journal of Respiratory and Critical Care Medicine. 2017; 195: 438–442.

[4] Battaglini D, Robba C, Ball L, Silva PL, Cruz FF, Pelosi P, *et al*. Noninvasive respiratory support and patient self-inflicted lung injury in COVID-19: a narrative review. British Journal of Anaesthesia. 2021; 127: 353–364.

[5] Palumbo D, Campochiaro C, Belletti A, Marinosci A, Dagna L, Zangrillo A, *et al*. Pneumothorax/pneumomediastinum in non-intubated COVID-19 patients: differences between first and second italian pandemic wave. European Journal of Internal Medicine. 2021; 88: 144–146.

[6] Elabbadi A, Urbina T, Berti E, Contou D, Plantefève G, Soulier Q, *et al*. Spontaneous pneumomediastinum: a surrogate of P-SILI in critically ill COVID-19 patients. Critical Care. 2022; 26: 350.

[7] Tonelli R, Bruzzi G, Manicardi L, Tabbì L, Fantini R, Castaniere I, *et al*. Risk factors for pulmonary air leak and clinical prognosis in patients with COVID-19 related acute respiratory failure: a retrospective matched control study. Frontiers in Medicine. 2022; 9: 848639.

[8] Murayama S. Spontaneous pneumomediastinum and Macklin effect: overview and appearance on computed tomography. World Journal of Radiology. 2014; 6: 850–854.

[9] Angelini M, Belletti A, Landoni G, Zangrillo A, De Cobelli F, Palumbo D. Macklin effect: from pathophysiology to clinical implication. Journal of Cardiothoracic and Vascular Anesthesia. 2024; 38: 881–883.

[10] Belletti A, Pallanch O, Bonizzoni MA, Guidi L, De Cobelli F, Landoni G, *et al*. Clinical use of Macklin-like radiological sign (Macklin effect): a systematic review. Respiratory Medicine. 2023; 210: 107178.

[11] Palumbo D, Zangrillo A, Belletti A, Guazzarotti G, Calvi MR, Guzzo F, *et al*. A radiological predictor for pneumomediastinum/pneumothorax in COVID-19 ARDS patients. Journal of Critical Care. 2021; 66: 14–19.

[12] Belletti A, Palumbo D, Zangrillo A, Fominskiy EV, Franchini S, Dell'Acqua A, *et al*. Predictors of pneumothorax/pneumomediastinum in mechanically ventilated COVID-19 patients. Journal of Cardiothoracic and Vascular Anesthesia. 2021; 35: 3642–3651.

[13] Paternoster G, Belmonte G, Scarano E, Rotondo P, Palumbo D, Belletti A, *et al*. Macklin effect on baseline chest CT scan accurately predicts barotrauma in COVID-19 patients. Respiratory Medicine. 2022; 197: 106853.

[14] Casadiego Monachello FJ, de la Torre Terron MC, Mendez Barraza JA, Casals Vila S. Macklin effect as an early radiological predictor of barotrauma in ARDS COVID-19 patients in invasive mechanical ventilation. Medicina Intensiva. 2023; 47: 235–236.

[15] Maccarrone V, Liou C, D'souza B, Salvatore MM, Leb J, Belletti A, *et al*. The Macklin effect closely correlates with pneumomediastinum in acutely ill intubated patients with COVID-19 infection. Clinical Imaging. 2023; 97: 50–54.

[16] Paternoster G, Bertini P, Belletti A, Landoni G, Gallotta S, Palumbo D, *et al*. Venovenous extracorporeal membrane oxygenation in awake non-intubated patients with COVID-19 ARDS at high risk for barotrauma. Journal of Cardiothoracic and Vascular Anesthesia. 2022; 36: 2975–2982.

[17] Vetrugno L, Castaldo N, Fantin A, Deana C, Cortegiani A, Longhini F, *et al*. Ventilatory associated barotrauma in COVID-19 patients: a multicenter observational case control study (COVI-MIX-study). Pulmonology. 2023; 29: 457–468.

[18] Valente Barbas CS, Marini Isola A, Baldisserotto S. Worsening COVID-19 acute respiratory distress syndrome: pneumomediastinum? Critical Care Medicine. 2023; 51: 145–148.

[19] Boussarsar M, Protti A. Pulmonary air leak in COVID-19: time to learn from our mistakes. Intensive Care Medicine. 2022; 48: 1614–1616.

[20] Ciceri F, Beretta L, Scandroglio AM, Colombo S, Landoni G, Ruggeri A, *et al*. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. Critical Care and Resuscitation. 2020; 22: 95–97.

[21] Grotberg JC, Hyzy RC, De Cardenas J, Co IN. Bronchopleural fistula in the mechanically ventilated patient: a concise review. Critical Care Medicine. 2021; 49: 292–301.

[22] Mauri T, Yoshida T, Bellani G, Goligher EC, Carteaux G, Rittayamai N, *et al*. Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. Intensive Care Medicine. 2016; 42: 1360–1373.

[23] Tonelli R, Fantini R, Tabbì L, Castaniere I, Pisani L, Pellegrino MR, *et al*. Early inspiratory effort assessment by esophageal manometry predicts noninvasive ventilation outcome in de novo respiratory failure. A pilot study. American Journal of Respiratory and Critical Care Medicine. 2020; 202: 558–567.

[24] Jonkman AH, Telias I, Spinelli E, Akoumianaki E, Piquilloud L. The oesophageal balloon for respiratory monitoring in ventilated patients: updated clinical review and practical aspects. European Respiratory Review. 2023; 32: 220186.

[25] Sartini C, Tresoldi M, Scarpellini P, Tettamanti A, Carcò F, Landoni G, *et al*. Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. JAMA. 2020; 323: 2338–2340.

[26] Li J, Luo J, Pavlov I, Perez Y, Tan W, Roca O, *et al*. Awake prone positioning for non-intubated patients with COVID-19-related acute hypoxaemic respiratory failure: a systematic review and meta-analysis. The Lancet Respiratory Medicine. 2022; 10: 573–583.

[27] Stilma W, Åkerman E, Artigas A, Bentley A, Bos LD, Bosman TJC, *et al*. Awake proning as an adjunctive therapy for refractory hypoxemia in non-intubated patients with COVID-19 acute respiratory failure: guidance from an international group of healthcare workers. American Journal of Tropical Medicine and Hygiene. 2021; 104: 1676–1686.

[28] Pasin L, Dagna L, Consonni M, Boraso S, Munari M, Romero García CC, *et al*. Prone positioning in awake COVID-19 patients: a systematic review and meta-analysis. Signa Vitae. 2023; 19: 31–36.

[29] Belletti A, Sofia R, Cicero P, Nardelli P, Franco A, Calabrò MG, *et al*. Extracorporeal membrane oxygenation without invasive ventilation for respiratory failure in adults: a systematic review. Critical Care Medicine. 2023; 51: 1790–1801.

[30] Murselović T, Berić S, Makovšek A. Pitfalls of difficult extubation in the

ICU; when is the right time to extubate a patient? Signa Vitae. 2024; 20: 22–26.

[31] Belletti A, D'Andria Ursoleo J, Piazza E, Mongardini E, Paternoster G, Guarracino F, *et al*. Extracorporeal membrane oxygenation for prevention of barotrauma in patients with respiratory failure: a scoping review. To be published in Artificial Organs. 2024. [Preprint].

[32] Tonna JE, Abrams D, Brodie D, Greenwood JC, Rubio Mateo-Sidron JA, Usman A, *et al*. Management of adult patients supported with venovenous extracorporeal membrane oxygenation (VV ECMO): guideline from the extracorporeal life support organization (ELSO). ASAIO Journal. 2021; 67: 601–610.

[33] Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators; Cavalcanti AB, Suzumura ÉA, Laranjeira LN, Paisani DM, Damiani LP, Guimarães HP, *et al*. Effect of lung recruitment and titrated Positive End-Expiratory Pressure (PEEP) *vs* low PEEP on mortality in patients with acute respiratory distress syndrome—a randomized clinical trial. JAMA. 2017; 318: 1335–1345.

[34] McNamee JJ, Gillies MA, Barrett NA, Perkins GD, Tunnicliffe W, Young D, *et al*. Effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal vs standard care ventilation on 90-day mortality in patients with acute hypoxemic respiratory failure: the REST randomized clinical trial. JAMA. 2021; 326: 1013–1023.

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